REMARKS

Claims 1-50 are pending in this application. Claims 1, 14, 23, 32, 38, 45 and 48 have been amended to indicate that methods of present invention comprises identifying the labeling moiety based on the mass defect of at least a portion of the labeling moiety. Support for such amendments can be found throughout the specification including, for example, page 9, lines 12-27. New Claim 51 has been added to specifically indicate that the mass spectrum data analysis comprises analyzing the mass spectrum peak corresponding to the mass defect of at least a portion of the labeling moiety. New Claims 52-58 have been added to indicate that methods of the present invention can be used in conjunction with other known methods. Support for such amendments can be found, for example, on page 22, line 32 to page 23, line 6.

Upon entry of this Amendment and Response Claims 1-58 will be pending in this application.

Rejection under 35 USC §112

Claims 13 and 23-31 are rejected under 35 USC §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regards as the invention. In particular, it appears the Office Action is alleging the term "mass defect" is "repugnant to the usual meaning of that term."

Applicants respectfully request reconsideration of this rejection as persons of ordinary skill would have no difficulty understanding the meaning of the term "mass defect." Accordingly, the claims are definite within the meaning of § 112. *In re Mercier*, 185 USPQ 774 (CCPA 1975) (claims sufficiently define an invention so long as one of ordinary skill can determine what subject matter is or is not within the scope of the claims).

The term "mass defect" is well known to one skilled in the art and refers to the difference between the actual mass of the nucleus (e.g., protons and neutrons) and

the theoretical mass of the nucleus. (See, for example, Exhibit A, which is a print-out of http://www.amershamhealth.com/medcyclopaedia/Volume%20I/MASS%20DEFECT.asp). The difference in the actual nucleus mass and the theoretical nucleus mass arises due to the binding energy that is required to hold protons and neutrons in close proximity in the nucleus. For example, the mass of a proton is 1.00728 amu and the mass of a neutron is 1.00866 amu. The standard in mass spectrum is that one atom of ^{12}C, the isotope of carbon with 6 protons and 6 neutrons, has a mass of exactly 12 amu. However, if one adds up the individual mass of 6 protons and 6 neutrons, the total theoretical mass of ^{12}C is 12.09564 amu, which is more than the actual 12 amu. In fact, the actual mass of any nucleus having two or more nucleons is less than the sum of its parts (i.e., theoretical mass or the sum of separate masses of its protons and neutrons). This difference in mass, i.e., "mass defect", is due to a conversion of some of the mass into the nucleus binding energy.

The term "mass defect" is also defined on page 690 of Bueche, Principles of Physics, 3rd edition (McGraw-Hill, NY, 1977) and has previously been used in other issued US Patents. For example, see U.S. Patent No. 6,287,780, issued September, 11, 2001. Therefore, it is submitted that the term "mass defect" is not indefinite. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 USC §112, second paragraph.

Rejection under 35 USC §102(b)

Claims 1, 2, 4, 7-15, 17-25, 28, 30-33, 36-38, 41-43, 45-46 and 48-50 are rejected under 35 USC §102(b) as allegedly being anticipated by US Patent No. 5,174,962, issued to Brennan.

It is axiomatic that claims are anticipated if, and only if, each and every element as set forth in the claim is found in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051 (Fed. Cir. 1989). Furthermore, "[t]he identical invention must be shown in as complete detail as is contained in the...claim." *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913 (Fed. Cir. 1989). See also, *PPG*

Industries Inc. v. Guardian Industries Corp., 7 USPQ2d 1618, 1624 (Fed. Cir. 1996). ("To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter.").

Brennan discusses the use of stable isotopes and isotope ratios of naturally-occurring elements in nucleotide bases for distinguishing peaks corresponding to sequencing ladders in mass spectrum. See, for example, Col. 6, lines 34-45. In particular, Brennan discusses discrimination of unnatural levels of stable isotopes or isotope ratios as the detection method.

As amended, claims of the present invention comprise the use of the mass defect as a means to discriminate ions of interest in the mass spectrum. As stated above, the term "mass defect" refers to the difference between the actual mass of the nucleus (e.g., protons and neutrons) and the theoretical mass of the nucleus, which results from the conversion of some of the mass into a nucleus binding energy. For example, while in theory ^{32}S and $^{16}O_2$ should have the same mass (both contain a total of 16 protons and 16 neutrons), the actual mass of ^{32}S is 31.9720707 and the actual mass of $^{16}O_2$ is 31.989829244 (2 x 15.994914622). See Handbook of Chemistry and Physics 81st ed., page 1-15, which is enclosed herewith as Exhibit B for the convenience of the Examiner. Thus, there is a difference of 0.01775854 amu between ^{32}S and $^{16}O_2$. By using a high resolution mass spectrometer that is capable of resolving this difference, one can readily distinguish the difference between ^{32}S and $^{16}O_2$.

Similarly, methods of the present invention use a labeling moiety that can be readily identified due to the mass defect of at least a portion of the labeling moiety. For example, when a fluorinated labeling moiety is used in conjunction with a high-resolution mass spectrometer, hydrogenated hydrocarbon moieties whose integral mass is 100, will have a fractionally higher actual mass, whereas the fluorinated labeling moiety whose integral mass is 100 will tend to have a fractionally lower actual mass. These differences in actual mass are readily distinguishable in a high accuracy (i.e., resolution) mass analysis.

Thus, two molecules with the same integral mass but different compositions will produce distinct peaks in the mass spectrum, if they have different degrees of hydrogen and fluorine. The fluorinated moieties are said to have a "mass defect". Since fluorinated moieties are not common in living systems, this means that a fluorinated labeling moieties will be readily distinguishable in the mass spectrum even in the presence of contaminating peaks due to fragmentation of the nucleic acids or of components from buffers and other reagents as long as the nucleic acids and reagents used are not fluorinated. Therefore, incorporation of a number of units of mass defect moieties, such as fluorinated aryl ethers, is a simple means of introducing a mass defect into the labeling moiety.

Brennan does not disclose using a mass defect of the labeling moiety in identifying or analyzing the fragments or the samples. Therefore, it is submitted that the rejection under 35 USC §102(b) is improper. Accordingly, Applicants respectfully request withdrawal of this rejection.

Rejection under 35 USC §103(a)

Claims 3, 5, 6, 16, 27, 34, 44, 47 and 50 are rejected under 35 USC §103(a) over Brennan in view of Meyer et al. (US Patent No. 6,359,111, issued March 19, 2002, hereinafter the "Meyer et al. patent").

In addition, Claims 26, 29, 35, 39 and 40 are rejected under 35 USC §103(a) over Brennan in view of Chait et al. (US Patent No. 6,391,649, issued May 21, 2002, hereinafter the "Chait et al. patent").

Neither the Meyer et al. patent nor the Chait et al. patent makes up the deficiencies in Brennan. Specifically, neither the Meyer et al. patent nor the Chait et al. patent discloses using a mass defect of the labeling moiety in identifying or analyzing the fragments or the samples. Therefore, without even commenting on the merits of combining the references in a manner suggested in the Office Action, it is submitted that the combination of the references does not lead to the methods of the present invention.

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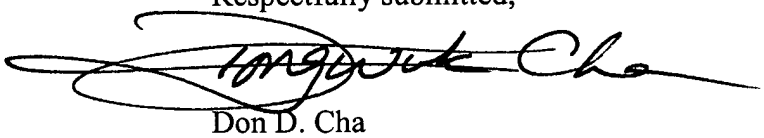
Accordingly, Applicants respectfully request withdrawal of all the rejections under 35 USC §103(a).

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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Mass defect, printer-friendly format

difference between the mass of the nucleus as a whole and the sum of the component nucleon masses.

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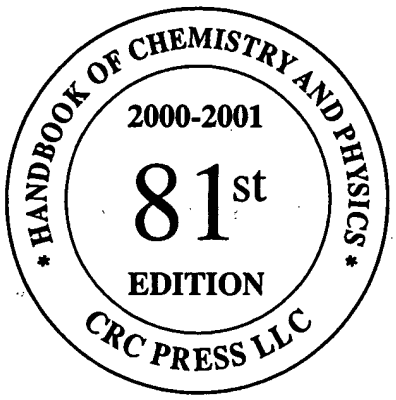
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ATOMIC MASSES AND ABUNDANCES

This table lists the mass (in atomic mass units, symbol u) and the natural abundance (in percent) of the stable nuclides and a few important radioactive nuclides. A complete table of all nuclides may be found in Section 11 ("Table of the Isotopes").

The atomic masses were taken from the 1995 evaluation of Audi and Wapstra (References 2, 3). Mass values were rounded in accordance with the stated uncertainty. The number in parentheses following the mass value is the uncertainty (specifically, the rounded value of the estimated standard deviation) in the last digit given.

Natural abundance values are also followed by uncertainties in the last digit(s) of the stated values. This uncertainty includes both the estimated measurement uncertainty and the reported range of variation in different terrestrial sources of the element. A * in the Abundance column indicates a radioactive nuclide not present in nature or an element whose isotopic composition varies so widely that a meaningful natural abundance cannot be defined. See Reference 5 for the most recent updates and further details on natural abundance.

REFERENCES

1. Holden, N. E., "Table of the Isotopes", in Lide, D. R., Ed., *CRC Handbook of Chemistry and Physics, 81st Ed.*, CRC Press, Boca Raton, FL, 2000.
2. Audi, G. and Wapstra, A. H., *Nucl. Phys.*, A595, 409, 1995.
3. Audi, G. and Wapstra, A. H., Atomic Mass Data Center, World Wide Web site, <http://csnwww.in2p3.fr>. Note that the print version in Reference 2 gives mass excess in energy units but not the actual atomic mass. The latter is included in the electronic version.
4. IUPAC Commission on Atomic Weights and Isotopic Abundances, *Pure Appl. Chem.*, 63, 991, 1991.
5. Rosman, K.J.R. and Taylor, P.D.P., *J. Phys. Chem. Ref. Data*, 27, 1275 (1998).

Z	Isotope	Mass in u	Abundance in %
1	^{1}H	1.007 825 032(1)	99.985(1)
1	^{2}H	2.014 101 778(1)	0.015(1)
1	^{3}H	3.016 049 268(1)	*
2	^{3}He	3.016 029 310(1)	0.000137(3)
2	^{4}He	4.002 603 250(1)	99.999863(3)
3	^{6}Li	6.015 122 3(5)	7.5(2)
3	^{7}Li	7.016 004 0(5)	92.5(2)
4	^{9}Be	9.012 182 1(4)	100
5	^{10}B	10.012 937 0(3)	19.9(2)
5	^{11}B	11.009 305 5(5)	80.1(2)
6	^{12}C	12 by definition	98.90(3)
6	^{13}C	13.003 354 838(1)	1.10(3)
6	^{14}C	14.003 241 988(4)	*
7	^{14}N	14.003 074 005(1)	99.634(9)
7	^{15}N	15.000 108 898(1)	0.366(9)
8	^{16}O	15.994 914 622(2)	99.762(15)
8	^{17}O	16.999 131 5(2)	0.038(3)
8	^{18}O	17.999 160 4(9)	0.200(12)
9	^{19}F	18.998 403 21(8)	100
10	^{20}Ne	19.992 440 176(2)	90.48(3)
10	^{21}Ne	20.993 846 74(4)	0.27(1)
10	^{22}Ne	21.991 385 5(2)	9.25(3)
11	^{23}Na	22.989 769 7(2)	100
12	^{24}Mg	23.985 041 9(2)	78.99(3)
12	^{25}Mg	24.985 837 0(2)	10.00(1)
12	^{26}Mg	25.982 593 0(2)	11.01(2)
13	^{27}Al	26.981 538 4(1)	100
14	^{28}Si	27.976 926 533(2)	92.23(1)
14	^{29}Si	28.976 494 72(3)	4.67(1)
14	^{30}Si	29.973 770 22(5)	3.10(1)
15	^{31}P	30.973 761 5(2)	100
16	^{32}S	31.972 070 7(1)	95.02(9)
16	^{33}S	32.971 458 5(1)	0.75(4)
16	^{34}S	33.967 866 8(1)	4.21(8)
16	^{36}S	35.967 080 9(3)	0.02(1)
17	^{35}Cl	34.968 852 71(4)	75.77(7)
17	^{37}Cl	36.965 902 60(5)	24.23(7)
18	^{36}Ar	35.967 546 3(3)	0.337(3)
18	^{37}Ar	36.966 775 9(3)	*
18	^{38}Ar	37.962 732 2(5)	0.063(1)
18	^{39}Ar	38.964 313(5)	*
18	^{40}Ar	39.962 383 123(3)	99.600(3)
19	^{39}K	38.963 706 8(3)	93.2581(44)
19	^{40}K	39.963 998 7(3)	0.0117(1)
19	^{41}K	40.961 826 0(3)	6.7302(44)
20	^{40}Ca	39.962 591 1(3)	96.941(18)
20	^{42}Ca	41.958 618 3(4)	0.647(9)
20	^{43}Ca	42.958 766 8(5)	0.135(6)
20	^{44}Ca	43.955 481 1(9)	2.086(12)
20	^{46}Ca	45.953 693(3)	0.004(3)
20	^{48}Ca	47.952 534(4)	0.187(4)
21	^{45}Sc	44.955 910(1)	100
22	^{46}Ti	45.952 629(1)	8.0(1)
22	^{47}Ti	46.951 764(1)	7.3(1)
22	^{48}Ti	47.947 947(1)	73.8(1)
22	^{49}Ti	48.947 871(1)	5.5(1)
22	^{50}Ti	49.944 792(1)	5.4(1)
23	^{50}V	49.947 163(1)	0.250(2)
23	^{51}V	50.943 964(1)	99.750(2)
24	^{50}Cr	49.946 050(1)	4.345(13)
24	^{52}Cr	51.940 512(2)	83.789(18)
24	^{53}Cr	52.940 654(2)	9.501(17)
24	^{54}Cr	53.938 885(1)	2.365(7)
25	^{55}Mn	54.938 050(1)	100
26	^{54}Fe	53.939 615(1)	5.8(1)
26	^{56}Fe	55.934 942(1)	91.72(30)
26	^{57}Fe	56.935 399(1)	2.1(1)
26	^{58}Fe	57.933 280(1)	0.28(1)
27	^{59}Co	58.933 200(2)	100
28	^{58}Ni	57.935 348(2)	68.077(9)
28	^{60}Ni	59.930 791(2)	26.223(8)
28	^{61}Ni	60.931 060(2)	1.140(1)
28	^{62}Ni	61.928 349(2)	3.634(2)
28	^{64}Ni	63.927 970(2)	0.926(1)
29	^{63}Cu	62.929 601(2)	69.17(3)
29	^{65}Cu	64.927 794(2)	30.83(3)
30	^{64}Zn	63.929 147(2)	48.6(3)
30	^{66}Zn	65.926 037(2)	27.9(2)